DETAILED ACTION

RESPONSE TO REMARKS

The Examiner thanks Applicants for their timely reply filed on 1 February 2010, in the matter of 10/591,004.

Applicants' election of Group I (claims 1-32, 37-45 and 69) **without traverse** is acknowledged.

The restriction requirement is hereby made **FINAL**. The remaining claims 33-36, 46-58, 63-68 and 70-77 (Groups II-IV) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Applicants timely traversed the revived restriction requirement between the compositions and method claims.

Thus, claims 1-32, 37-45 and 69 are presented and represent all claims under consideration.

INFORMATION DISCLOSURE STATEMENT

Two Information Disclosure Statement (IDS), filed 30 October 2006 and 17 December 2007, are acknowledged and have been considered.

CLAIM REJECTIONS - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-16 and 29-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-16 and 29-32 each recite the limitation "wherein the controlled release coating" in each of the claims. There is insufficient antecedent basis for this limitation in claim 1 for the limitation recited in claims 13-16 and insufficient antecedent basis for this limitation in claim 17 for the limitation recited in claims 29-32.

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, 15, 17, 19, 31 and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Frantsits et al. (USPN 6,500,455; also published as WO 00/59508).

The instant invention is drawn to an oral, controlled-release composition of tolperisone comprising an enantiomeric mixture of tolperisone or one of its salts, in combination with a controlled release agent (claims 1, 5, 17 and 19). With regard to the release profile limitations recited by claims 1, 5, 17 and 19; until some material difference(s) in the properties of the composition are demonstrated, said limitations are considered by the Examiner as being directed toward the instantly claimed compositions. Claim 3 further limits the enantiomeric mixture of tolperisone such that it is a racemic

mixture (i.e. a mixture of R- and S-tolperisone). Claims 15 and 31 recite that the controlled release coating is pH dependent. Claim 69 recites that the enantiomeric mixture of tolperisone contains at least 50 wt% of R-tolperisone and no less than (e.g. at least) 10 wt% of S-tolperisone. A (50/50) (R/S) mixture of tolperisone is considered as reading on this limitation.

The teachings of Frantsits are directed to oral, tolperisone-containing pharmaceutical preparations (Title), wherein the active tolperisone is in the form of a 50/50 racemic mixture which is liberated from the preparation in the body in a delayed manner and preferably in the intestinal canal (Abstract). This teaching is considered as being anticipatory, namely because a delayed release is indicative of an additional controlled release agent as evidenced by the Examples provided by Frantsits. Furthermore, release of the drug being pH-dependent is necessarily taught in light of the preferred teaching of release taking place in the intestinal canal (i.e. a portion of the gastrointestinal tract which is known to vary in pH). Thus, in order to obtain targeted release within the intestines is dependent upon the environmental pH. Thus, the reference meets each of the instant limitations.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4, 6-10, 20-26, 37-38 and 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frantsits et al. as set forth above with respect to claims 1 and 17, in further view of Szelenyi et al. (US Pre-Grant Publication N° 2005/0089559).

The limitations of claims 1 and 17 are discussed above. The composition of claim 3 is respectively further limited such that the controlled release dosage form comprises 100-249 mg (claim 4) or 250-500 mg (claim 7) of the racemic mixture of tolperisone. Similarly, the composition of claim 17 is respectively further limited such that the controlled release dosage form comprises 100-249 mg (claim 20) or 250-500 mg (claim

23) of the racemic mixture of tolperisone. Independent claim 37 recites a combination of the limitations of claims 1 and 4, wherein the controlled release composition of tolperisone comprises 100-200 mg of racemic tolperisone. Similarly, independent claim 41 recites a combination of the limitations of claims 1, 4 and 7, wherein the controlled release composition of tolperisone comprises 201-500 mg of racemic tolperisone. With regard to the release profile limitations recited in claims 6, 8-10, 21, 22, 24-26, 37-38 and 41-43; until some material difference(s) in the properties of the compositions are demonstrated, said limitations are considered by the Examiner as being directed toward the instantly claimed compositions.

The teachings of Frantsits et al. are discussed above. Despite providing several examples employing a 50/50 racemic mixture of tolperisone in solid controlled release dosage forms, Frantsits does not expressly disclose how much tolperisone any of the dosages contain. However, such values with respect to the claimed composition are considered by the Examiner as being adjustable and further, that it would be well within the purview of the ordinarily skilled artisan to routinely optimize such an amount. Turning to the prior art, the ordinarily skilled artisan would be highly motivated to prepare a dosage form containing the instantly claimed amounts of tolperisone particularly in light of the teachings of Szelenyi et al., which expressly disclose the preferred daily dose of tolperisone as ranging from 150-450 mg tolperisone per day in adults. Szelenyi's silence to the racemic nature of tolperisone is interpreted by the Examiner as the dosage range being applicable to all forms of tolperisone. Thus, it would have been customary for an

artisan of ordinary skill, to modify the preparations taught by Frantsits to contain the instantly claimed amounts of tolperisone, in order to achieve the desired composition. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

Claims 2, 11-16, 18 and 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frantsits et al. as set forth above with respect to claims 1 and 17, further in combination with Ishibashi et al. (US Pre-Grant Publication N° 2003/0012815).

The limitations to claims 1 and 17 are discussed above. Claims 2 and 18 recite additional structural limitations to the base claims first wherein the core of the composition comprises not only the enantiomeric mixture of tolperisone, but also the controlled release agent, and second, wherein said core is encased within a controlled release coating. The limitations of claims 11-16 and 27-32 are drawn to further defining the controlled release agent, in general and in terms of the coating.

The teachings of Frantsits are discussed above. Of particular note is that the Examples are drawn to solid, coated particles of racemic tolperisone that release the drug in a delayed manner, preferably in the intestines. The reference is deficient in that the core is not expressly disclosed as being additionally combined with excipients. The delayed release of the active is also not further disclosed as being attributed to such polymers as Eudragit blends "L", "RS" or mixtures of the two.

The invention practiced by Ishibashi is directed to a layered release drug formulation comprising a drug-containing core substance and a multilayered coating which may comprise different hydrophobic organic compound-water-soluble polymer mixtures (Abstract). The reference further discloses the core as being comprised of the drug and various types of additives in order to establish a medicated core particle ¶[0062]. Drugs which are disclosed as being encapsulated in the practiced dosage form include muscle relaxants such as tolperisone HCl ¶[0063]. Additives are also disclosed ¶[0064]. Concerning the coating of the particles, Ishibashi expressly teaches that at least one coating layer is employed which itself comprises water-soluble, water-insoluble enteric polymers or mixtures thereof ¶[0065]. Such a layer is included according to Ishibashi in order to protect the encapsulated drug, for "adjusting the rate of release more efficiently, [or] enhancing resistance to stomach acidity" ¶[0074]. Examples of water-insoluble polymers include Eudragit® RS, whereas examples of enteric polymers include Eudragit® blends "L" and/or "S" ¶[0075].

In light of the forgoing, the ordinarily skilled artisan would have been motivated to modify the Frantsits composition mixing the core with release rate controlling additives as well as modifying the coating composition to employ the instantly claimed Eudragit® compounds, with the reasonable expectation of arriving at the instantly claimed composition. Such an expectation, absent a showing of evidence to the contrary is more than reasonable considering that the Eudragit polymers are well-established pH-independent and pH-dependent water-soluble and enteric based polymers which are used

to encapsulate and delay the release of active pharmaceutical agents within the gastrointestinal tract. The ordinarily skilled artisan would be further motivated to employ the aforementioned polymers with the Frantsits invention, particularly given that the goal of Frantsits is also to establish a solid, coated dosage form which delays its drug release until it enters the intestinal canal.

Thus, based on the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonably high expectation of successfully producing the instantly claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence of evidence to the contrary.

Claims 39-40 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Frantsits et al. and Szelenyi et al., as set forth above with respect to claims 37 and 41, respectively, in further combination with Ishibashi et al.

The limitations of claims 37 and 41 are discussed above. Claims 39 and 44 recite the same structural limitations as claims 2 and 18 such that the core component comprises a mixture of the racemic tolperisone and a controlled release agent wherein said core is further encapsulated by a controlled release coating composition. With regard to the release limitations recited in claims 40 and 45; until some material difference(s) in the properties of the composition are demonstrated, said limitations are considered by the Examiner as being directed towards the instantly claimed composition.

The teachings of Frantsits, Szelenyi and Ishibashi are all discussed above.

Concerning the combined teachings of Frantsits and Ishibashi, neither reference expressly discloses the amount of tolperisone which may be incorporated into the core of the coated particles. However, the Szelenyi reference remedies this deficiency, as discussed above, specifically stating that the preferred adult daily doses of tolperisone will range between 150-450 mg of tolperisone. Further motivation to combine the teachings of Szelenyi with Frantsits and Ishibashi is found in that preferred oral dosage forms of Szelenyi include controlled release forms such as delayed release formulations ¶[0046].

Thus, based on the combined teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence of evidence to the contrary.

All claims have been rejected; no claims are allowed.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for

the organization where this application or proceeding is assigned is 571-273-8300.

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